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# Palladium-catalyzed C–H activation of anilides at room temperature: *ortho*-arylation and acetoxylation†

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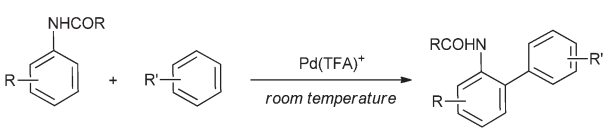
**Room-temperature *ortho*-arylation and acetoxylation of anilides have been achieved using cationic palladium ($Pd[TFA]^+$) as catalyst and $(NH_4)_2S_2O_8$ as oxidant. Preliminary investigation of the mechanism suggests that palladium may have different oxidation states in the catalytic cycles of these two transformations.**

Chelation-assisted palladium-catalyzed direct C–H arylation has emerged as a promising strategy for the regioselective construction of biaryl linkages in the past decade.[1,2] However, those transformations frequently encounter elevated temperature (often more than 100 °C), which may limit their application to the synthesis of more delicate molecules. In recent years, a number of coupling reactions between arenes bearing directing groups and organic halides or surrogates, or organometallic reagents (C–H/C–X type) have been achieved at room temperature.[3] However, the more challenging yet efficient oxidative C–H/C–H cross-coupling reactions, which do not need the preactivation of both coupling partners, have rarely been realized at ambient temperature probably due to the low reactivity of C–H bonds. In 2006, a pioneering work of Lu and co-workers disclosed the first palladium-catalyzed oxidative cross-coupling of two simple arenes at room temperature, albeit with low catalytic efficiency and limited substrate scope.[4] Very recently, a room-temperature dehydrogenative cross-coupling reaction between *N*-methoxybenzamides and arenes was involved in the first step for the synthesis of phenanthridinones.[5]

Cationic palladium species have been found to be highly reactive catalysts towards aryl C–H bond activation due to their high electrophilicity.[6] Among these catalysts, $Pd(TFA)^+$ generated *in situ* from $Pd(OAc)_2$ and trifluoroacetic acid (TFA) is the most effective and widely used one.[7] A variety of $Pd(TFA)^+$-catalyzed C–H functionalizations of arenes have been achieved at ambient temperature, including the addition to C–C multiple bonds,[7b,c] the carboxylation,[8] the decarboxylative acylation,[9] and the above-mentioned oxidative cross-coupling of two simple arenes.[4] Encouraged by the pioneering work, we reasoned that the utilization of cationic palladium as catalyst could realize the dehydrogenative coupling reaction of simple arenes with arenes bearing electron-rich directing groups at room temperature. The high electrophilicity of cationic palladium species might be beneficial to the metalation of both coupling partners.

Amides are electron-rich functional groups that are widely used to direct the highly regioselective *ortho*-functionalization of aromatic rings.[10] Given the importance of arylated anilides in the synthesis of valuable aniline derivatives,[11] we herein report a $Pd(TFA)^+$-catalyzed dehydrogenative cross-coupling of anilides with arenes at room temperature using low-cost, easy-to-handle, and environmentally friendly $(NH_4)_2S_2O_8$ as oxidant (Scheme 1). In addition, this catalytic system is successfully extended to the room-temperature acetoxylation of anilides. Of particular note is that *no exclusion of air or moisture is required in these transformations.*

The $Pd(TFA)^+$-catalyzed oxidative C–H/C–H cross-coupling of pivalanilides with arenes have been successively reported by Buchwald[10g] and Dong,[10h] who employed $O_2$ as the oxidant at 80–100 °C and $Na_2S_2O_8$ as the oxidant at 70 °C, respectively. However, the removal of the pivaloyl group is often difficult after the coupling reaction. In contrast, the acetyl group of the arylated acetanilides could be readily removed under basic conditions.[11c] Thus, our study mainly focused on acetanilides and the coupling reaction of *N*-(*o*-tolyl)acetamide **1a** with *o*-xylene **2c** was first used to optimize the conditions. It was found that the best result of 95% yield was obtained by using 10 mol% of $Pd(OAc)_2$ as catalyst,




**Scheme 1** Electrophilic $Pd^{2+}$ catalyzed dehydrogenative cross-coupling of anilides with arenes.

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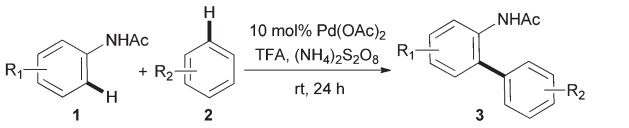
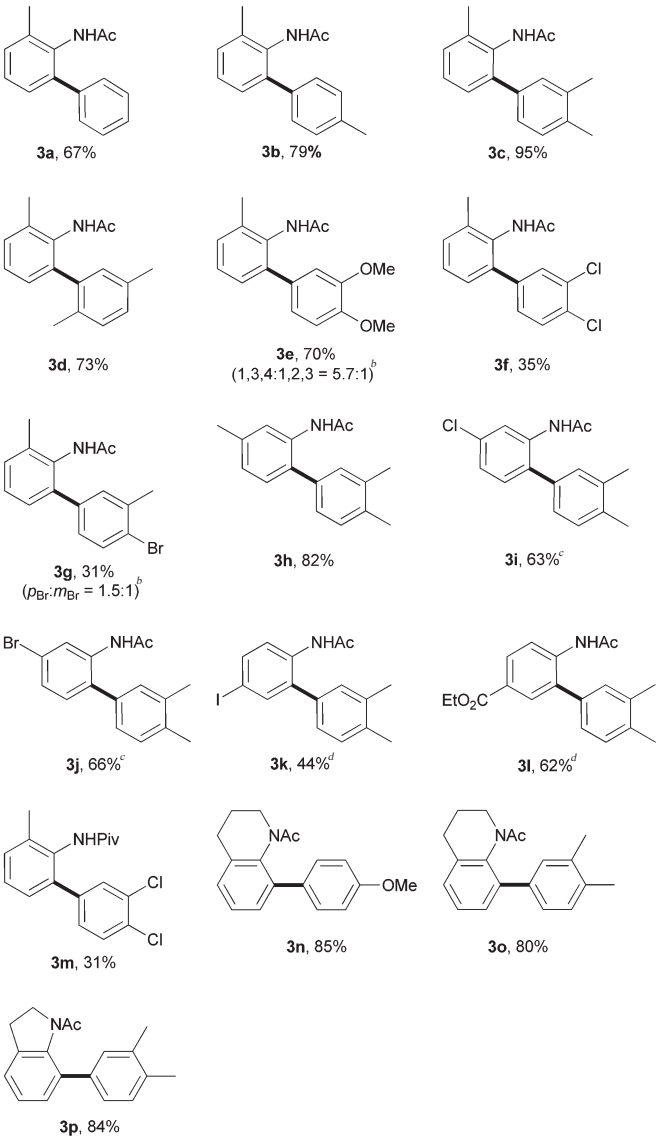
20.0 equiv of TFA as acid, and 2.0 equiv of $(NH_4)_2S_2O_8$ as oxidant (ESI†, Table S1, entry 3). Control experiments showed that the reaction was totally ineffective in the absence of either $Pd(OAc)_2$ or TFA (ESI†, Table S1, entries 15 and 16). Replacing TFA with HOAc, PivOH or $HBF_4$ gave the desired product **3c** in less than 16% yield (ESI†, Table S1, entries 9–11), showing the superiority of $Pd(TFA)^+$ to other cationic palladium species. Reducing the amounts of $Pd(OAc)_2$ to 5 mol%, TFA to 10.0 equiv or *o*-xylene to 10.0 equiv could all give the coupling product **3c**, albeit with slightly lower efficiency (ESI†, Table S1, entries 12–14).

With the optimized conditions in hand, the scope of this room-temperature dehydrogenative coupling reaction with respect to anilides and arenes was then examined (Table 1). Arenes with neural or electron-rich substituents smoothly coupled with *N*-(*o*-tolyl)acetamide **1a** to give the arylated products in good yields of up to 95% (Table 1, **3a–3e**). However, the reaction of arenes bearing electron-withdrawing groups such as 1,2-dichlorobenzene and 1-bromo-2-methylbenzene afforded the desired products in low yields of 35% and 31%, respectively (Table 1, **3f** and **3g**). The use of 1,2-dimethoxybenzene and 1-bromo-2-methylbenzene as coupling partners resulted in the formation of two regioisomers as an inseparable mixture (Table 1, **3e** and **3g**). Surprisingly, when monosubstituted arenes such as toluene and anisloe were used as the substrates, only their *para*-arylated products were obtained (Table 1, **3b** and **3n**). It was noteworthy that not only chlorine and bromine atoms, but also iodine substituents on acetanilides were compatible with the current catalytic conditions, demonstrating the high chemoselectivity of this reaction towards C–H activation (Table 1, **3i–3k**). The acetanilide bearing a second potential directing group such as ester also showed high regioselectivity and the desired product arylated at the *ortho* position of amide was obtained in 62% yield (Table 1, **3l**). In addition, other anilides such as pivalanilides, *N*-acetyl-1,2,3,4-tetrahydroquinolines and *N*-acetyl-2,3-dihydroindoles all smoothly coupled with arenes and their reaction efficiencies were comparable to acetanilides (Table 1, **3m–3p**). Unfortunately, arenes with other electron-rich chelating groups such as aryl ureas, *O*-phenylcarbamates and phenol esters failed to give the desired arylated products in synthetically useful yields.

Next, the feasibility of this catalytic system to other C–H functionalization reactions was investigated. Phenols are widely found in natural products, medicines, and argochemicals.[12] Although many methods have been developed for the synthesis of phenol derivatives by the transition-metal-catalyzed C–H oxygenation of arenes,[10j,13] rare examples have been realized at room temperature.[10j,13k] Previously reported acetoxylation of acetanilides catalyzed by $Pd(OAc)_2$ at 100 °C offered a good platform to test the catalytic capability of the $Pd(TFA)^+/(NH_4)_2S_2O_8$ system described herein.[13f] Thus, the reaction of *N*-phenylacetamide **1b** with HOAc rather than arenes was attempted under otherwise identical conditions to the arylation reaction. Pleasantly, the acetoxylated product **4a** was obtained in 41% yield. Further optimization increased the yield of **4a** to 67% by reducing the amount of TFA to 5.0 equiv (Table 2, **4a**). Subsequently, it was found that a variety of acetanilides with methyl, ester, and halogen substituents could all give the acetoxylated products in synthetically useful yields (Table 2, **4b–4f**). When acetanilide was substituted with a strong electron-withdrawing nitro group, the product was obtained in a low yield

**Table 1** Scope of the *ortho*-arylation of anilides at room temperature[a]

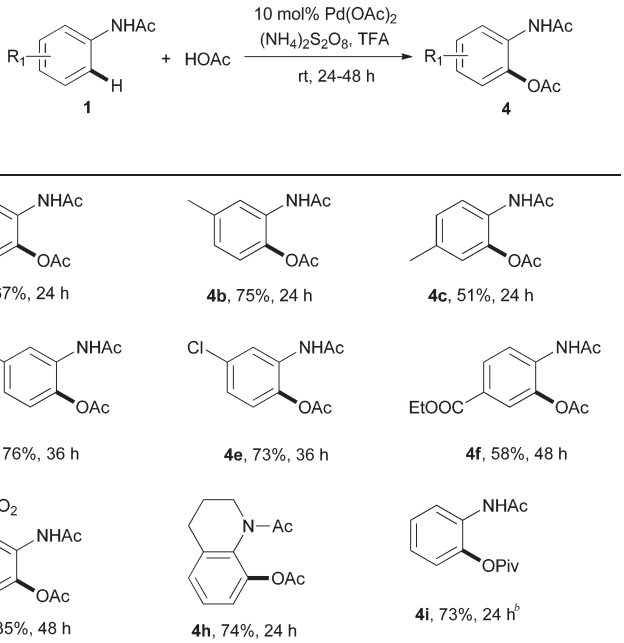



[a] Reaction conditions: anilide (0.5 mmol, 1.0 equiv), arene (10.0 mmol, 20.0 equiv), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), TFA (10.0 mmol, 20.0 equiv), $(NH_4)_2S_2O_8$ (1.0 mmol, 2.0 equiv), r.t., 24 h. Isolated yield. [b] Yield for the mixture of two regioisomers. Ratio of the two isomers determined by $^1H$ NMR is given in the parentheses. [c] 36 h. [d] $(NH_4)_2S_2O_8$ (1.5 mmol, 3.0 equiv), 48 h.

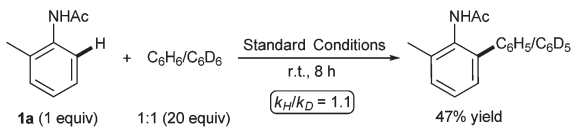
**Table 2** Palladium-catalyzed *ortho*-acetoxylation of acetanilides at room temperature[a]




[a] Reaction conditions: acetanilide (0.5 mmol, 1.0 equiv), HOAc (10.0 mmol, 20.0 equiv), $Pd(OAc)_2$ (0.05 mmol, 10 mol%), TFA (2.5 mmol, 5.0 equiv), $(NH_4)_2S_2O_8$ (1.0 mmol, 2.0 equiv), r.t.. Isolated yield. [b] HOPiv instead of HOAc was used. HOPiv = pivalic acid.

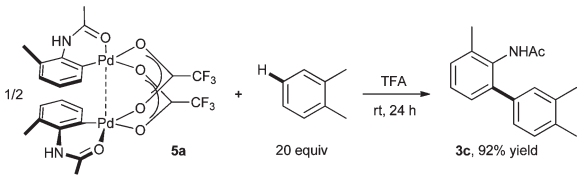
of 35% (Table 2, **4g**). Notably, the pival group could also be introduced to the *ortho* position of acetanilides simply by replacing HOAc with HOPiv (Table 2, **4i**).

To gain some insight into the mechanism, the competition reaction between benzene and deuterated benzene was conducted for 8 h. As shown in eqn (1), no kinetic isotope effect was observed for benzene ($k_H/k_D$ = 1.1), illustrating that the C–H bond cleavage of simple arenes might proceed *via* an electrophilic palladation mechanism and it was not involved in the rate-limiting step of the *ortho*-arylation reaction of acetanilides.



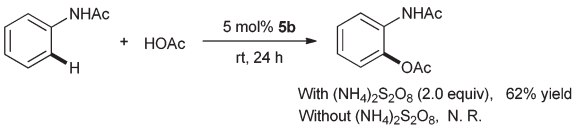
(1)

Furthermore, the palladium complexes **5a** and **5b** with trifluoroacetate anion were synthesized from $Pd(OAc)_2$, TFA, and *N*-(*o*-tolyl)acetamide **1a** or *N*-phenylacetamide **1b** at room temperature by following the modified literature procedure (See ESI† for details).[10h,14] The exposure of complex **5a** to *o*-xylene and TFA at room temperature resulted in the formation of **3c** in 92% yield (eqn (2)), implying that complex **5a** might be the truly active catalytic species. No $(NH_4)_2S_2O_8$ was needed for this transformation, indicating that a Pd(II)/Pd(0) catalytic cycle might be involved in the process.



(2)

To our surprise, the reaction of the complex **5b** with HOAc failed to yield the acetoxylated product. It was suspected that the presence of anilide substrates in the reaction system might help dimeric Pd complexes to dissociate and thus facilitate the acetoxylation reaction.[15] Treatment of *N*-phenylacetamide **1b** with 5 mol% of **5b** and 2.0 equiv of $(NH_4)_2S_2O_8$ did afford the desired product **4a** in 62% yield (eqn (3)). However, no reaction happened in the absence of $(NH_4)_2S_2O_8$. Given the high redox potential of $(NH_4)_2S_2O_8$ (2.01 V),[16] it was possible that Pd(II) was oxidized to the hexacoordinated Pd(IV) intermediate in the acetoxylation reaction.[13c,f]



(3)

In conclusion, the electrophilic $Pd(TFA)^+$-catalyzed direct *ortho*-arylation and acetoxylation of acetanilides have been realized at room temperature using $(NH_4)_2S_2O_8$ as oxidant. Both transformations are operationally simple and no exclusion of air/moisture is required. On the basis of preliminary studies, it is possible that these two reactions proceed *via* different mechanisms with the arylation involving a Pd(0)/Pd(II) catalytic cycle and the acetoxylation involving a Pd(II)/Pd(IV) catalytic cycle.

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